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Description

The invention relates to an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally. More specifically, the invention relates to an implant of such small dimensions that it can be fitted subcutaneously with an ordinary hypodermic needle.

There is a large demand for the development of new, long-acting contraceptives which require a minimum of medical guidance. This is valid in particular for those areas of the world where the medical infrastructure is poor, and where family planning can be organized only to an insufficient extent.

Contraceptive implants are known in the art. For example, in Robertson et al. Chemical Abstracts, vol. 99, no. 8, abstr. no. 99:5884p (1983), covered rods having a core rod of drug and filler-free polydimethylsiloxane polymer (50:50, wt./wt.) sealed inside thin-walled silastic tubing are disclosed. See also Robertson Long Acting Contraceptive Delivery Systems, Chap. 11, "Implantable Levonorgestrel Rod Systems: In Vivo Release Rates and Clinical Effects", pp. 133 - 139 (1983), U.S. Patent No. 3,903,880 to Higuchi et al., epecially EXAMPLE 1, and EP-A-200,224.

An implant of this type, which can release a contraceptive agent in virtually constant quantities over a period of at least 2 years, but preferably for about 4 to 5 years, is a new development which can certainly supply what is needed. The great problem, however, is that the often large amount of the contraceptive agent with which the polymeric material of the implant has to be charged to guarantee release for about 4 years leads to very large implants which can only be fitted surgically, or to several smaller implants which have to be fitted simultaneously.

The need for subcutaneous fitting of a plurality of (smaller) implants also offers little attraction at the present time.

In theory any polymeric material is suitable for the development of an implant provided only that it is biologically compatible, and also any material with a progestational action. In this context reference may be made, for example, to U.S. Patent No. 3,279,996 (Long et al.) in which an implant is described which contains an active substance encased by a polysiloxane membrane, and to Dutch Patent 167,850 (Zaffaroni) in which an implant is described in which the active substance is contained in a polymer, and this polymer loaded with active substance is encased by a polymer membrane which completely controls the rate of release. However, if a limit is set to the dimensions of the implant, if a certain amount of implant rigidity is required to facilitate introduction, and, furthermore, if the achievement of a release duration of the contraceptive substance of a minimum of 2 years, and preferably of up to 4 to 5 years, is desired, then all available theoretical solutions seem to fail.

The implant of the invention can be considered one of the release systems known per se which consist of a core of active material encased by a release rate-regulating membrane. The choice of polymers to be used, the choice of the contraceptive substances, and the dimensions of the implant are, however, matched in such a way that a unique release system is obtained which complies completely with the requirements stipulated above.

The implant of the invention is cylindrical or virtually cylindrical with a maximum section of about 2 mm, but preferably between 1,5 and 2.0 mm, and possesses a variable length. The length of the implant will, however, not exceed about 5 cm for practical reasons. The length is preferably between 1 and 4 cm. These dimensions of the implant of the invention are so small that subcutaneous fitting can be carried out with an ordinary hypodermic needle.

The implant of the invention is characterized by:

a) core material of ethylene/vinyl acetate copolymer (hereafter called EVA) having such a molecular weight that the melt index is higher than 10 gram per 10 minutes, and a vinyl acetate content of 20% by weight or more; which core material functions as a matrix for 3-keto-desogestrel, levonorgestrel or gestodene as active contraceptive substances, in a quantity which is sufficient for a long-lasting constant release of at least 15 µg of active substance per day, and

b) a membrane having a layer thickness of 50-250 µm which encases the core material and also consists of EVA material, but with such a molecular weight that the melt index is less than 10 gram per 10 minutes, and an acetate content of less than 20% by weight,

this implant being completely or virtually completely cylindrical with a maximum external diameter of about 2 mm and a length which is smaller than about 5 cm.

The contraceptively active substance, which can be employed in the context of the present invention, is a highly active progestagen, particularly 3-keto-desogestrel, levonorgestrel or gestodene. These contraceptive substances are highly active substances which show already an effective progestational action with a daily dosage of about 15-30 µg.

This core material can be charged to about 75 percent by weight with the active substance without seriously affecting the utility of the EVA core material. However, a degree of charging of about 50-60% by weight is preferred.

The core material used in the present invention is an EVA polymer with a melt index higher than 10 gram/10 min. and preferably between 25 and 30 g/10 min. The vinyl acetate content of the core material is higher than 20% by weight and preferably higher than 25% by weight.

Very suitable EVA polymers which can be used as core material are, for example, Evatane(R) with the designations 28-150, 28-399, and 28-400, supplied by ICI and 28.420 and in particular 28.25 and 33.25 supplied by Atochem, and Elvax(R) with the designations 310, 250, 230, 220, and 210, supplied by Du Pont de Nemours.

The membrane polymer is also an EVA polymer which, however, has a higher molecular weight than that of the core material. The melt index of this membrane material is less than 10 g/10 min., and preferably less than or equal to 8 g/10 min.; the vinyl acetate content is less than 20% by weight.

Suitable EVA polymers which can be used as a membrane are, for example, Evatane(R) with the designations 501/502 (melt index 2, vinyl acetate content 7.5%), 554/555 (4, 12.5%), 540 (10, 18%) and particularly 571 (8, 15%), Elvax(R) with the designations 450, 460, 470, 550, 560, 650, 660, 670, 750, 760 and 770, and Evatane(R) 1080 VN 5 and in particular 1040 VN 4 supplied by Atochem.

The release characteristic of the contraceptive substance (through the membrane) is determined to a large extent by the vinyl acetate content of the EVA membrane.

The implant of the invention is obtained by means of a so-called co-axial extrusion process, a method in which the two EVA polymers are extruded co-axially in preset layer thicknesses with the aid of a co-axial extrusion head.

This co-axial extrusion process means that both polymers are transported in the molten state through the co-axial extrusion head, the molten core material at the same time containing the active substance.

Due to this co-axial extrusion process a contact layer is produced on the interface of the two polymers, which layer is probably fully or partially responsible for the outstanding drug-release properties of the co-extrudate, but in any event prevents the two polymer layers working loose from each other after a period of time, due to disappearance of the active substance from the core polymer, which loosening would fundamentally disturb the release pattern.

The co-axial extrusion process is art known per se so that it will not be gone into further within the scope of this description.

A thick, co-axial filament with a maximum external diameter of about 2 mm, and preferably between about 1,5 and 2.0 mm, is obtained by means of the co-axial extrusion process. The filament is then cut into pieces up to a maximum of about 5 cm long, using conventional techniques.

Although certainly not necessary the circular ends of the implant may - if desired - be additionally protected by an inert polymer, for example polyethylene, polypropylene or the EVA polymer which is used for the membrane, or also, for example, by a (medical grade) silicone adhesive. This protective layer is obtained, for example, by dipping the surface into a smelt or solution of the particular polymer. If necessary, the end can also be singed or pinched closed.

An other embodiment of the implant of the invention possesses a thin layer of polysiloxane around the whole external surface of the implant described above, in addition to the assembly as described above. This polysiloxane is chosen so that the release pattern is not influenced to any appreciable extent; the formation of a second release-rate-regulating layer is thus not intended by this. The layer in question can therefore be extremely thin, even of the order of about 20-50 μm; a somewhat thicker layer, however, is just as permissible.

This protective layer can be obtained by dipping or immersing the implant in a thin tubing of polysiloxane.

The implant of the invention should in each case contain a sufficient quantity of active substance when used for application in humans Which is such that it can bring about virtually constant release of the active substance for a minimum of 1 year, which roughly means that the core material must be charged with 5 to 15 mg of 3-keto-desogestrel, levonorgestrel or gestodene. An additional quantity of active substance of about 5 to 15 mg is necessary for each additional year in which the implant must release, so that a quantity of 25-75 mg of active material can be needed for a release duration of 5 years.

The implant of the invention is preferably be used as a subcutaneous implant, but may also be applied locally, e.g. in the uterine or cervical region.

Example 1

The active substance 3-keto-desogestrel and EVA core material (melt index 400 g/10 min., vinyl acetate content 28% by weight)-Evatane(R) 28-400 - were mixed in a ratio of 1:1 (on a weight basis) on a heatable mill at a temperature of 80 °C. The polymer sheets charged with 3-keto-desogestrel were reduced in size and then processed into pellets by means of an extruder and a so-called chopper.

The pellets charged with 3-keto-desogestrel intended for the core, and EVA pellets intended for the membrane (melt index 8 g/10 minutes; vinyl acetate content 15% by weight, Evatane(R) 571), were transferred to two separate hoppers of the co-axial extrusion apparatus. The co-axial filament was extruded at a temperature of about 100 °C. A co-axial filament with an external diameter of 1.9 mm and a skin thickness of 150 µm was obtained with a correct choice and a correct adjustment of the spinneret geometry, the feed rates of the core and skin material to the spinneret, and the winding rate of the fibre. The extruded co-axial filament was cooled in a water bath, and then wound onto bobbins with a draw rate of 0.25 N. The extrusion rate of the filament was 2.3 metres per sec. Typical preparation conditions:

	Temperature (°C)	Pressure (bar)
Extruder (barrel)	100	60 → 173
Extruder (core)	80	5 → 46
Spinneret	100	

The extruded co-axial filament was then cut into the required length. The filament pieces were wrapped in polysiloxane if desired using polysiloxane tubing (dimensions 1.57/2.41 mm internal/external diameter) to be swelled in cyclohexane and thereafter to be filled with the co-axial filament of the required length, and finally dried under vacuum. The two ends of the implant obtained were sealed with silicone adhesive (medical grade). The external diameter of the implant provided with a polysiloxane layer was 2.5 mm, the external diameter of the implant not provided with a polysiloxane layer was 1.9 mm.

The in vitro release of 3-keto-desogestrel from this implant was tested in 250 ml demineralized water at 37 °C. This medium was contained in a 300 ml conical flask which was shaken at 150 cyles/minute with an amplitude of 2.5 cm.

Results

Table 1

In vitro release of 3-keto-desogestrel from a 3 cm implant with and without a polysiloxane external layer.

Day	Release (µg/day.cm)	
	without polysiloxane layer	with polysiloxane layer
1	10.0	6.7
2	10.7	9.7
3	11.3	10.0
4	10.3	9.7
7	10.3	9.3
9	10.0	9.7
10	10.0	9.7
14	10.3	9.7

The polysiloxane external layer here has practically no influence on the released pattern.

Table 2

In vitro release of 3-keto-desogestrel from an implant (3 cm) prepared in this way and provided with a polysiloxane layer. The implant was sterilized by heat treatment (20 min, 120 °C).

Day	Release (μg/day.cm)
2	57.0*
5	14.7
10	10.3
20	11.3
30	10.3
40	10.0
50	10.0
90	9.0
100	9.3
200	8.7
300	8.3
376	8.3
400	7.7
471	7.7

500	8.0
550	7.7
600	8.0
650	7.0
700	6.3
750	6.0
800	6.3

* boost of 3-keto-desogestrel because of heat sterilization.

Table 3

In vivo release:

Average plasma concentrations (3 dogs) of 3-keto-desogestrel after subcutaneous introduction of an implant prepared in this way (see implant of table 2).

Day	Plasma concentration (pmol/ml)
1	2.11*
2	0.81
3	0.62
7	0.66
14	0.46
21	0.53
28	0.49
35	0.56
42	0.56
51	0.56
56	0.54
63	0.59
70	0.60
77	0.59
84	0.59
91	0.63

* boost of 3-keto-desogestrel because of heat sterilization.

Example 2

The active substance 3-keto-desogestrel and Evatane(R) 28-400 were blended in 1:1 weight ratio in a 10 mm extruder at a temperature of 100 °C.

The extrudate obtained was granulated with the acid of a pelletizer, after which the pellets were heated in vacuo at 135 °C for one hour.

In the same manner as described in Example 1 a co-axial filament was extruded using the above 3-keto-desogestrel charged pellets as core material and uncharged Evatane(R) 571 pellets as membrane material.The membrane thickness of the co-axial fibre was 135 μm, and the external diameter of the implant was 1.65 mm. The dimensions of the polysiloxane tubing were: 1.47 (internal) x 1.95 mm (external diameter). The ends of the 4-cm long implant were sealed with medical grade silicone adhesive. The external diameter of an implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation conditions of the relevant co-axial filament:

	Temperature (° C)	Pressure (bar)
Extruder (barrel)	80 → 100	50 → 160
Extruder (core)	70 → 85	60 → 70
Spinneret	100	

Table 4

In vitro release of 3-keto-desogestrel from this 4 cm long implant. The implant was gamma-sterilized (25 kGy).

Day	Release (µg/day.cm)
1	10.0*
2	7.8
3	7.8
4	7.5
10	8.0
20	7.8
30	7.3
40	7.3
50	7.3
100	6.0
150	6.5
200	6.0
250	5.5
300	5.8
350	5.3
400	5.0
450	4.6
500	4.3
550	4.0

* boost of 3-keto-desogestrel is minimal as gamma sterilization was used instead of heat sterilization.

Example 3

Analogous to Example 2, a co-axial filament was spun, but in this case with a membrane thickness of 90 µm. The external diameter of the implant was also about 1.65 mm in this case. Polysiloxane tubing (1.47 x 1.95 mm) was again used for the polysiloxane jacket and the ends were sealed with medical-grade

silicone adhesive. The external diameter of the implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation condition of the co-axial filament.

	Temperature (° C)	Pressure (bar)
Extruder (barrel)	75 → 100	160 → 150
Extruder (core)	60 → 100	150 → 110
Spinneret	125	

The length of the implant was 3 cm.

Table 5

In vitro release of 3-keto-desogestrel from this non-sterilized implant:	
Day	Release (µg/day.cm)
1	13.7
6	9.7
9	9.7
10	10.7
20	10.7
30	9.3
40	9.0
50	8.7
60	9.7
70	9.3
80	9.0
90	9.3
100	8.3
110	9.0

Example 4

Co-axial filament was obtained according to the method described in Example 2.

The filament consists of Evatane(R) 28.25 as core material and Evatane(R) 1040 VN 4 as the membrane material.

Further data: membrane thickness: 75 µm;
core material charged with 60% (wt) 3-keto-desogesterel;
external diameter of the implant: 1.7 mm;
length implant: 3,0 cm;
polysiloxane jacket up to external diameter : 2,05 mm;
sealing of the implant ends with silicone adhesive.

Table 6

In vitro release from the non sterilised implant:	
Day	Release (µg/day.cm)
1	24.7
5	22.0
10	13.7
20	12.8
30	12.3
40	11.0
50	11.3
60	11.3
70	11.0
80	11.0
90	10.7
100	10.3
110	10.3
120	8.3
130	10.0
140	8.7
150	8.3
160	9.3

Example 5

Same procedure and material as described in Example 4.

Specifications: core material: Evatane(R) 28.25;
membrane: Evatane(R) 1040 VN 4
membrane thickness: 60 µm
core charged with 60% (wt) 3-keto desogestrel;
externel diameter: 2,0 mm;
length: 4,0 cm;
no polysiloxane jacket;
no sealing of implant ends.

Table 7

In vitro release:	
Day	Release (µg/day.cm)
1	43.9
5	27.8
10	24.9
20	21.3
30	21.1
40	18.9
50	19.1
60	17.4
70	15.4
80	16.1
90	18.5
100	16.8
110	16.5
120	16.3

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Implant with contraceptive action intended for subcutaneous or local administration, characterized by:
   a) core material of ethylene/vinyl acetate copolymer (hereinafter called EVA) having such a molecular weight that the melt index is higher than 10 gram per 10 minutes, and a vinyl acetate content of 20% by weight or more, which core material functions as a matrix for 3-keto-desogestrel, levonorgestrel or gestodene as the active contraceptive substance in a quantity which is sufficient for a longlasting constant release of at least about 15 µg of active substance per day, and
   b) a membrane having a layer thickness of 50-250 µm which encases the core material and also consists of EVA material, but with such a molecular weight that the melt index is less than 10 gram/10 minutes, and a vinyl acetate content of less than 20% by weight, this implant being completely or virtually completely cylindrical with a maximum external diameter of about 2 mm and a length which is smaller than about 5 cm.

2. Implant according to claim 1, characterized in that it is obtained by co-axial extrusion of the two EVA polymers.

3. Implant according to claims 1 and 2, characterized in that an EVA polymer is used as core material with a melt index between 25 and 30 gram/10 min. and a vinyl acetate content of more than 25% by weight.

4. Implant according to claims 1 and 2, characterized in that EVA material is used as membrane material with a melt index of less than or equal to 8 gram/10 min and a vinyl acetate content of less than 20% by weight.

5. Implant according to claims 1 and 2, characterized in that 3-keto-desogestrel is used as a contraceptive substance.

Claims for the following Contracting States : GR, ES

1. A method for manufacturing an implant comprising:
   mixing a core material of ethylene/vinyl acetate copolymer (hereinafter called EVA) having such a molecular weight that the melt index is greater than 10 grams/10 minutes, and a vinyl acetate content of at least 20% by weight with 3-keto-desogestrel, levonorgestrel or gestodene as active contraceptive substance in a quantity which is sufficient for a longlasting constant release of at least about 15 µg of

active substance per day;

and co-axially extruding said mixture with EVA having such a molecular weight that the melt index is less than 10 grams/10 minutes and a vinyl acetate content less than 20% by weight, thereby forming an implant having a core encased with a membrane having a layer thickness of 50-250µm, this implant being completely or virtually completely cylindrical with a maximum external diameter of about 2 mm and a length which is smaller than about 5 cm.

2. The method of claim 1, wherein the EVA used as core material has a melt index between 25 and 30 grams/10 minutes and a vinyl acetate content of greater than 25 % by weight.

3. The method of claim 1 or claim 2 wherein the EVA used as membrane has a a melt index of less than or equal to 8 grams/10 minutes and a vinyl acetate content of less than 20 % by weight.

4. The method of claim 1 or claim 2, characterized in that the implant contains 3-ketodesogestrel as the contraceptive substance.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Implantat mit empfängnisverhütender Wirkung, vorgesehen für subcutane oder örtliche Verabreichung, gekennzeichnet durch :

a) Kernmaterial aus Aethylen-/Vinylacetat-Copolymer (im folgenden EVA genannt), welches ein solches Molekulargewicht aufweist, dass der Schmelzindex höher ist als 10 Gramm pro 10 Minuten, und einen Vinylacetatgehalt von 20 Gewichtsprozent oder mehr aufweist, welches Kernmaterial als Matrix für 3-Keto-desogestrel, Levonorgestrel oder Gestoden als aktive empfängnisverhütende Substanz in einer Menge, welche genügt für eine langdauernde konstante Abgabe von mindestens etwa 15 µg aktiver Substanz pro Tag, dient, und

b) eine Membran mit einer Schichtdicke von 50 bis 250 µm, welche das Kernmaterial umhüllt und ebenfalls aus EVA-Material besteht, jedoch mit einem solchen Molekulargewicht, dass der Schmelzindex kleiner als 10 Gramm pro 10 Minuten beträgt, und einem Vinylacetatgehalt von weniger als 20 Gewichtsprozent, wobei dieses Implantat vollständig oder praktisch vollständig zylindrisch ist mit einem maximalen äusseren Durchmesser von etwa 2 mm und einer Länge, welche kleiner als etwa 5 cm ist.

2. Implantat nach Anspruch 1, dadurch gekennzeichnet, dass es durch koaxiale Extrusion der beiden EVA-Polymeren erhalten ist.

3. Implantat nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, dass ein EVA-Polymer mit einem Schmelzindex zwischen 25 und 30 Gramm pro 10 Minuten und einen Vinylacetatgehalt von mehr als 25 Gewichtsprozent als Kernmaterial verwendet wird.

4. Implantat nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, dass EVA-Material mit einem Schmelzindex von weniger als oder gleich 8 Gramm pro 10 Minuten und einem Vinylacetatgehalt von weniger als 20 Gewichtsprozent als Membranmaterial verwendet wird.

5. Implantat nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, dass 3-Keto-desogestrel als empfängnisverhütende Substanz verwendet wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines Implantates, umfassend :

das Vermischen eines Kernmaterials aus Aethylen-/Vinylacetat-Copolymer (im folgenden EVA genannt) mit einem derartigen Molekulargewicht, dass der Schmelzindex grösser als 10 Gramm pro 10 Minuten beträgt, und einen Vinylacetatgehalt von mindestens 20 Gewichtsprozent mit 3-Keto-desogestrel, Levonorgestrel oder Gastoden als aktive empfängnisverhütende Substanz in einer Menge, welches für eine langdauernde konstante Abgabe von mindestens etwa 15 µg aktive Substanz pro Tag genügt,

und coaxiale Extrusion dieses Gemisches mit EVA, welches ein solches Molekulargewicht, dass

der Schmelzindex weniger als 10 Gramm pro 10 Minuten beträgt, und einen Vinylacetatgehalt von weniger als 20 Gewichtprozent aufweist, wodurch ein Implantat gebildet wird mit einem Kern, der mit einer Membran umhüllt ist, welche eine Schichtdicke von 50 bis 250 µm aufweist, wobei dieses Implantat vollständig oder praktisch vollständig zylindrisch ist mit einem maximalen äusseren Durchmesser von etwa 2 mm und einer Länge, welche kleiner ist als etwa 5 cm.

2. Verfahren nach Anspruch 1, in welchem das als Kernmaterial verwendete EVA einen Schmelzindex zwischen 25 und 30 Gramm pro 10 Minuten und einen Vinylacetatgehalt von mehr als 25 Gewichtsprozent aufweist.

3. Verfahren nach Anspruch 1 oder 2, in welchem das als Membran verwendete EVA einen Schmelzindex von weniger als oder gleich 8 Gramm pro 10 Minuten und einen Vinylacetatgehalt von weniger als 20 Gewichtsprozent aufweist.

4. Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass das Implantat 3-Keto-desogestrel als die empfängnisverhütende Substanz enthält.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Implant à action contraceptive destiné à une administration sous-cutanée ou locale, caractérisé par :
   a) une matière de noyau consistant en copolymère éthylène/acétate de vinyle (appelé ci-après EAV) ayant un poids moléculaire tel que l'indice de fusion soit supérieur à 10 grammes par 10 minutes et une teneur en acétate de vinyle de 20 % en poids ou plus, cette matière de noyau servant de matrice pour le 3-cétodésogestrel, le lévonorgestrel ou le gestodène utilisé comme substance contraceptive active en une quantité qui est suffisante pour assurer une libération constante sur une longue durée d'au moins environ 15 µg de substance active par jour, et
   b) une membrane ayant une épaisseur de couche de 50 à 250 µm, qui entoure la matière de noyau et qui est également constituée de matière EAV, mais ayant un poids moléculaire tel que l'indice de fusion soit inférieur à 10 grammes/10 minutes et une teneur en acétate de vinyle inférieure à 20 % en poids,
   cet implant étant complètement ou presque complètement cylindrique avec un diamètre externe d'environ 2 mm au maximum et une longueur qui est inférieure à 5 cm environ.

2. Implant selon la revendication 1, caractérisé par le fait qu'il est obtenu par extrusion coaxiale des deux polymères EAV.

3. Implant selon les revendications 1 et 2, caractérisé par le fait que le polymère EAV utilisé comme matière de noyau a un indice de fusion compris entre 25 et 30 grammes/10 min et une teneur en acétate de vinyle d'au plus 25 % en poids.

4. Implant selon les revendications 1 et 2, caractérisé par le fait que la matière EAV utilisée comme matière de membrane a un indice de fusion inférieur ou égal à 8 grammes/10 min et une teneur en acétate de vinyle inférieure à 20 % en poids.

5. Implant selon les revendications 1 et 2, caractérisé en ce que le 3-cétodésogestrel est utilisé comme substance contraceptive.

Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de fabrication d'un implant qui consiste à :
   mélanger une matière de noyau consistant en copolymère éthylène/acétate de vinyle (désigné ci-après par EAV) ayant un poids moléculaire tel que l'indice de fusion soit supérieur à 10 grammes/10 minutes et une teneur en acétate de vinyle d'au moins 20 % en poids, avec du 3-cétodésogestrel, du lévonorgestrel ou du gestodène comme substance contraceptive en une quantité suffisante pour assurer une libération constante sur une longue durée d'au moins environ 15 µg de substance active par jour ; et
   extruder coaxialement ledit mélange avec un EAV ayant un poids moléculaire tel que l'indice de

fusion soit inférieur à 10 grammes/10 minutes et une teneur en acétate de vinyle inférieure à 20 % en poids, pour former ainsi un implant comportant un noyau entouré d'une membrane ayant une épaisseur de couche de 50 à 250 µm, cet implant étant complètement ou presque complètement cylindrique avec un diamètre externe d'environ 2 mm au maximum et une longueur qui est inférieure à 5 cm environ.

2. Procédé selon la revendication 1, dans lequel le EAV utilisé comme matière de noyau a un indice de fusion compris entre 25 et 30 grammes/10 minutes et une teneur en acétate de vinyle supérieure à 25 % en poids.

3. Procédé selon la revendication 1 ou 2, dans lequel le EAV utilisé comme membrane a un indice de fusion inférieur ou égal à 8 grammes/10 minutes et une teneur en acétate de vinyle inférieure à 20 % en poids.

4. Procédé selon la revendication 1 ou la revendication 2, caractérisé en ce que l'implant contient du 3-cétodésogestrel comme substance contraceptive.